NCCN Prostate Cancer Early Detection Guideline

Joan McClure
Senior Vice President
National Comprehensive Cancer Network
African American Prostate Cancer Disparity Summit
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What is NCCN?

- Alliance of 20 academic cancer centers in the United States
- Goal: Improve patient care
- Develop programs to support missions in education, research, patient care, and health information
- National Outcomes Research Network
NCCN Clinical Practice Guidelines--Goals

• Improve the quality of care for patients with cancer

• Reflect evolving data and treatment patterns by updating continuously

• Reinforce multidisciplinary interactions in oncology care

• Provide standard for evaluating cancer care in the United States
**NCCN Guidelines Program**

- Clinical practice guidelines for cancer
  - Risk reduction
  - Early detection
  - Treatment
  - Supportive care
- 48 panels consist of over 750 multidisciplinary cancer specialists
Guidelines Principles

- Ensure multidisciplinary input
- Evaluate available evidence
- Manage bias
- Develop consensus on appropriate recommendations
- Update continuously to reflect evolving data
- Measure adherence to guidelines
Prostate Cancer Early Detection Panel Composition

- Urologists
- Internists
- Epidemiologists
- Radiation oncologist
- Medical oncologist
- Biostatistician
- Pathologist
- Patient Advocate
# NCCN Prostate Cancer Early Detection Panel Members

<table>
<thead>
<tr>
<th>Name</th>
<th>Institution/Title</th>
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<tbody>
<tr>
<td>Richard J. Babaian, MD/Chair</td>
<td>The University of Texas M. D. Anderson Cancer Center</td>
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<td>Arthur G. James Cancer Hospital &amp; Richard J. Solove Research Institute at The Ohio State University</td>
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<td>Michael Barry, MD</td>
<td>Dana-Farber/Partners CancerCare</td>
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<td>Peter R. Carroll, MD</td>
<td>UCSF Comprehensive Cancer Center</td>
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<td>H. Ballentine Carter, MD</td>
<td>The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins</td>
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<td>William J. Catalona, MD</td>
<td>Robert H. Lurie Comprehensive Cancer Center of Northwestern University</td>
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<td>Jonathan I. Epstein, MD</td>
<td>The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins</td>
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<td>Ruth B. Etzioni, PhD</td>
<td>Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance</td>
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<td>Peter Gann, MD, ScD</td>
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<td>UNMC Eppley Cancer Center at The Nebraska Medical Center</td>
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<td>Richard J. Howe, PhD</td>
<td>Consultant</td>
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<td>Mark H. Kawachi, MD</td>
<td>City of Hope Cancer Center</td>
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<td>Name</td>
<td>Institution</td>
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<td>Jeff D. Kopin, MD</td>
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<td>Paul H. Lange, MD</td>
<td>Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance</td>
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<td>Hans Lilja, MD</td>
<td>Memorial Sloan-Kettering Cancer Center</td>
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<td>James Mohler, MD</td>
<td>Roswell Park Cancer Institute</td>
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<td>Robert B. Nadler, MD</td>
<td>Robert H. Lurie Comprehensive Cancer Center of Northwestern University</td>
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<tr>
<td>Alan Pollack, MD, PhD</td>
<td>Fox Chase Cancer Center</td>
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<tr>
<td>Julio M. Pow-Sang, MD</td>
<td>H. Lee Moffitt Cancer Center and Research Institute at the University of South Florida</td>
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<td>Joseph C. Presti, MD</td>
<td>Stanford Hospital &amp; Clinics</td>
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<td>Antoinette M. Stroup, PhD</td>
<td>Huntsman Cancer Institute at the University of Utah</td>
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<td>Donald A. Urban, MD</td>
<td>University of Alabama at Birmingham Comprehensive Cancer Center</td>
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<td>Johannes Vieweg, MD</td>
<td>Duke Comprehensive Cancer Center</td>
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<td>Robert Wake, MD</td>
<td>St. Jude’s Children’s Research Hospital/University of Tennessee Cancer Institute</td>
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<tr>
<td>John T. Wei, MD, MS</td>
<td>University of Michigan Comprehensive Cancer Center</td>
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Guidelines Development

• Evidence–based
• Consensus derived
Evidence

• There is inadequate evidence to base decisions on in many areas of oncology
• New studies WILL change the standard of care over time
• Continuous review of evidence and guideline updates are required
NCCN Consensus Process

- Review
- Iteration
<table>
<thead>
<tr>
<th>Category</th>
<th>Level of Evidence</th>
<th>Degree of Consensus</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>High</td>
<td>Uniform</td>
</tr>
<tr>
<td>2 A</td>
<td>Lower</td>
<td>Uniform</td>
</tr>
<tr>
<td>2 B</td>
<td>Lower</td>
<td>Non-uniform</td>
</tr>
<tr>
<td>3</td>
<td>Any</td>
<td>Major disagreement</td>
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NCCN Prostate Early Detection Guideline

- Does not make recommendation on whether or not to screen
- If screening is elected, the guideline recommends how to do it
The Controversy

• Screening identifies both clinically insignificant and clinically significant prostate cancers
• Not all prostate cancers require treatment; however, it is difficult to differentiate prospectively between those that do and those that don’t
• Treatment of clinically insignificant prostate cancers can result in significant morbidity
• Not treating clinically significant prostate cancers can result in advanced disease and death
<table>
<thead>
<tr>
<th>Guideline Developer</th>
<th>Recommend Screening?</th>
<th>Age to Begin Screening</th>
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<tbody>
<tr>
<td>NCCN</td>
<td>Silent</td>
<td>If screening elected baseline at 40</td>
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<tr>
<td>AUA</td>
<td>YES</td>
<td>50—normal risk 40—high risk</td>
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<tr>
<td>ACS</td>
<td>YES</td>
<td>50—normal risk 45—high risk</td>
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<tr>
<td>USPSTF</td>
<td>NO</td>
<td>NA</td>
</tr>
<tr>
<td>ACP</td>
<td>NO</td>
<td>NA</td>
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PROSTATE CANCER EARLY DETECTION
National Comprehensive Cancer Network
Clinical Practice Guidelines in Oncology 1.2006

BASELINE EVALUATION
H&P including:
- Family history
- Medications
- History of prostate disease and screening, including prior PSA and/or isoforms, exams and biopsies
- PSA velocity, if available

RISK ASSESSMENT
Start risk and benefit discussion
and
Offer baseline DRE and PSA at age 40 (category 2B)

SCREENING EVALUATION
PSA ≥ 0.6 ng/mL or African-American or Family history

FOLLOW-UP
Annual follow-up (category 2B):
- DRE
- PSA

PSA ≤ 0.6 ng/mL
Repeat at age 45

PSA < 0.6 ng/mL
Offer regular screening at age 50

PSA > 0.6 ng/mL
Annual follow-up (category 2B):
- DRE
- PSA

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a See Introduction (PROSD-1).
b The median value in 40-49 age range is 0.6 ng/mL.
c There is no evidence in the literature to support the follow-up recommendations listed; they represent the consensus-based opinions of the panel based upon their clinical experience.
d Family history may affect a decision to biopsy. The closer the relative, the earlier the onset and the more affected family members, the higher the risk.

PROSD-2
Baseline screening

- Discussion of risks and benefits of screening
- DRE and PSA
- At age 40—no good consensus about this age.
Results of Initial Screening

High risk groups

• Patients with baseline PSA ≤ 0.6 ng/ml, or
• African American, or
• Family history of prostate cancer especially at an early age

Normal risk group

• Patients with baseline PSA of < 0.6 ng/ml
• No other high risk characteristics
Family History of Prostate Cancer

- Father, brother, or son with prostate cancer
- Diagnosed at an early age
African American

- Higher incidence and higher mortality in this population
- Evidence of specific genotype linked to increased risk of prostate cancer especially at a younger age
• 3x greater rate of prostate cancer if PSA > median for age
• Risk increases as PSA level increases above the median especially in younger patients
• Higher than median PSA is associated with higher risk of aggressive disease and higher risk of recurrence following local therapy.
## PSA > Median for Age Group

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Median PSA</th>
<th>Risk of Prostate Cancer within 5 Years with PSA &lt; Median</th>
<th>Risk of Prostate Cancer within 5 years with PSA ≥ Median</th>
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</thead>
<tbody>
<tr>
<td>40-50</td>
<td>0.6-0.7</td>
<td>0.5%</td>
<td>7.3%</td>
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<tr>
<td>50-60</td>
<td>0.7-0.9</td>
<td>0.7%</td>
<td>8.1%</td>
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</table>

*Loeb, et al Urology, 2006*
Prostate cancer is being diagnosed earlier
More clinically insignificant cancers are being diagnosed (and treated)
Fewer patients are being diagnosed with metastatic disease
Follow-up

High Risk Patients: Annual follow-up with DRE and PSA—non uniform consensus

Normal Risk Patients: Repeat at age 45:

- If PSA < 0.6 ng/ml Offer regular screening at age 50
- If PSA ≥ 0.6 ng/ml: Annual follow-up with DRE and PSA—non uniform consensus
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Clinical Practice Guidelines in Oncology 1.2006

**DIAGNOSTIC EVALUATION**

- **DRE**
  - **Offer total PSA or complexed PSA**

**SCREENING RESULTS**

- **DRE negative**
  - **PSA not performed**

**FOLLOW-UP**

- **Annual DRE**

- **DRE positive regardless of PSA results**

- **TRUS-guided biopsy (See PROSD-8)**

- **See Follow-up (PROSD-4)**

- **DRE negative PSA performed**

- **See Screening Results and Follow-up (PROSD-5)**

**PROSD-3**
PSA

• Ejaculation:
  ➤ Results are more reliable if patient has abstained from ejaculation for 48 hr. If this condition is not met, repeat after 48 hr abstention, if the original sample was marginally elevated.

• Medicines that affect PSA:
  ➤ Finasteride
  ➤ Androgen receptor blockers
  ➤ Dutasteride

• If possible, draw PSA before DRE.
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SCREENING RESULTS

- PSA ≤ 2.5 ng/mL and PSA velocity < 0.5 ng/mL/y if available
  → Annual DRE and PSA

- PSA 2.6-4 ng/mL or PSA velocity ≥ 0.5 ng/mL/y when PSA ≤ 2.5 ng/mL
  → Consider biopsy

FOLLOW-UP

- PSA Velocity < 0.5 ng/mL/y
  → Continue follow-up

- PSA Velocity ≥ 0.5 ng/mL/y
  → Consider initial TRUS-guided biopsy

Cancer

TRUS-guided biopsy performed (See PROSD-8)

TRUS-guided biopsy not performed

ASAP or High-grade PIN

Negative or atypia not suspicious for cancer

6-12 mo follow-up with DRE, and total or complexed PSA; Consider percent free PSA if not using complexed PSA

See PSA 4 to 10 ng/mL (PROSD-6)

See PSA > 10 ng/mL (PROSD-7)
Use of free PSA in considering initial biopsy:

- ≤ 10%  Biopsy
- 10 - 25%  Consider biopsy
- > 25%  Consider deferring biopsy
**PROSTATE CANCER EARLY DETECTION**

**Clinical Practice Guidelines in Oncology 1.2006**

**SCREENING RESULTS**

- TRUS-guided biopsy (preferred) (See PROSD-8)
- Percent free PSA in selected patients where risk of biopsy and/or diagnosis and treatment is outweighed by comorbid conditions

**FOLLOW-UP**

- Negative → 6-12 mo follow-up with DRE, and total or percent complexed or percent free PSA
- Positive → See NCCN Prostate Cancer Treatment Guidelines

- Biopsy (See PROSD-8)
- PSA 4-10 ng/mL

- Biopsy (See PROSD-8)
- ≤ 10% → Biopsy (See PROSD-8)
- > 10 ≤ 25% → Follow-up with DRE and total or percent complexed PSA, or percent free PSA (category 2B)
- > 25% → Annual follow-up with DRE, total PSA, and percent free PSA

PROSD-6
PROSTATE CANCER EARLY DETECTION
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Percent free PSA $\leq 10\%$
- Repeat biopsy
  - Biopsy positive → See NCCN Prostate Cancer Treatment Guidelines
  - Biopsy negative → 6-12 mo follow-up with DRE, and total or percent complexed or percent free PSA including PSAV

Percent free PSA $10 \leq 25\%$
- Discuss rebiopsy or
- Follow-up with DRE, total or percent complexed PSA, or percent free PSA

Percent free PSA $> 25\%$
- 6-12 mo follow-up with DRE, and total or percent complexed or percent free PSA including PSAV

PROSD-6
PROSTATE CANCER EARLY DETECTION

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SCREENING RESULTS

- PSA > 10 ng/mL → Biopsy
- Negative or atypia not suspicious for cancer → Consider rebiopsy timing interval 3-12 mo based on doctor-patient discussion
- ASAP or High-grade PIN

FOLLOW-UP

- Negative → 6-12 mo follow-up with DRE, and total or percent complexed or percent free PSA including PSAV; Consider a 3rd biopsy based on individual patient parameters and choice
- Positive → See NCCN Prostate Cancer Treatment Guidelines

See NCCN Prostate Cancer Treatment Guidelines

See TRUS-guided biopsy (PROSD-8)
FOLLOW-UP FOR TRUS BIOPSIIES

Positive → See NCCN Prostate Cancer Treatment Guidelines

ASAP suspicious for cancer → Extended pattern rebiopsy (within 3 mo) with increased sampling of ASAP site and adjacent areas. If no cancer found, close follow-up with PSA and DRE

High-grade PIN → If initial sextant biopsy used, rebiopsy using extended pattern, including transition zone

Negative or atypia not suspicious for cancer → If extended pattern used initially, immediate repeat biopsy is probably not necessary within the first year; consider delayed repeat biopsy using extended strategy

Follow-up, based on DRE and PSA findings:
- Positive DRE (See PROSD-4)
- High Risk (See PROSD-5)
- PSA 4-10 (See PROSD-6)
- PSA > 10 (See PROSD-7)

If no cancer found, close follow up with PSA and DRE
TRUS-GUIDED BIOPSY

Initial and Repeat
Extended-pattern biopsy (12 cores)
• Number of Cores:
  › Sextant (6) and,
  › Lateral peripheral zone (6) and,
  › Lesion-directed at palpable nodule or suspicious image
• Transition zone biopsy is not supported in routine biopsy. However, the addition of a transition zone biopsy to an extended biopsy protocol may be considered in a repeat biopsy if PSA is persistently elevated.
• After 2 negative extended TRUS biopsies, prostate cancer is not commonly found at repeat biopsy.
• For high risk men with multiple negative biopsies, consideration can be given to a saturation biopsy strategy.
• Local anesthesia can decrease pain/discomfort associated with prostate biopsy.
SUGGESTED “TALKING POINTS” TO COVER IN A DISCUSSION WITH A POTENTIAL SCREEENEE ABOUT THE PROS AND CONS OF PSA TESTING

• Prostate cancer is the most common cancer found in older men, other than skin cancer. Men in the United States have about 1 chance in 6 of eventually finding out they have prostate cancer. Men who have regular PSA tests have a higher chance of finding out they have prostate cancer; men who do not have PSA tests have a lower chance but a higher probability of having more advanced cancer when ultimately diagnosed. The PSA test can detect the majority of prostate cancers earlier than a digital rectal examination when a man has no symptoms.

• African-American men and men with a father, brother, or son with prostate cancer (especially if it was found at a younger age) have a higher risk of prostate cancer. Latino men have a slightly lower risk, while Native American, and Asian-American men have a substantially lower risk.

• American men also have about 1 chance in 30 of eventually dying from prostate cancer. However, this would be higher, if no men opted for early detection and treatment. About 30,000 men die from prostate cancer each year in the United States. Only about 1 in 100 prostate cancer deaths occur in men under age 55. About 1 in 20 prostate cancer deaths occur in men age 55-64, 2 in 10 in men age 65-74, and 7 in 10 in men age 75 and older. However, these deaths usually occur after some period of suffering from metastatic disease.
SUGGESTED “TALKING POINTS” TO COVER IN A DISCUSSION WITH A POTENTIAL SCREEENEE ABOUT THE PROS AND CONS OF PSA TESTING

• Many prostate cancers grow very slowly. Consequently, many men with prostate cancer may die of something else before their prostate cancer causes any symptoms. However prostate cancers that grow more rapidly can potentially impact overall survival and quality of life. Whether a man will die of something else or prostate cancer depends on how aggressive the cancer is, how early it is detected, how effectively it is treated, as well as a man’s age and his other medical problems. Most experts believe that in general men over age 75, or even younger men with serious medical problems, have little to gain from a PSA test.

• Doctors disagree about what level of PSA is high enough to do further testing, such as a prostate biopsy, to look for prostate cancer. Most doctors feel men with PSA levels greater than 4 should have a biopsy, while others feel men with levels greater than 2.5 should have a biopsy. There is an increasing tendency to focus less on absolute PSA values and to consider changes in PSA over time. There is accumulating evidence that men who have a steady rise in their PSA level are more likely to have cancer, and if the rise is rapid, the cancer is more likely to be life threatening. Other factors such as patient age and prostate volume (how large the gland is) are also important to consider when deciding who needs a prostate biopsy.
PROSTATE CANCER EARLY DETECTION
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SUGGESTED “TALKING POINTS” TO COVER IN A DISCUSSION WITH A POTENTIAL SCREENER ABOUT THE PROS AND CONS OF PSA TESTING

• A prostate biopsy is usually performed using local anesthesia through a probe placed into the rectum through which a needle is placed. This needle is used to take samples of the prostate tissue. Usually 10 to 12 samples are taken. The prostate biopsy, not the PSA test, tells whether or not a man has prostate cancer. A prostate biopsy is usually well tolerated and infrequently causes serious problems such as pain, infection or bleeding in the urine, semen, or stool. Long-term complications almost never occur.

• A PSA test can be abnormal even when a man does not have prostate cancer. This is called a “false positive” test. These false positive PSA tests can come from other prostate conditions that are not important to find (unless a man has bothersome urinary symptoms). About 1 out of 3 men with a high PSA level have prostate cancer, which means that 2 out of 3 do not. The higher the PSA level, the more likely a man will be found to have prostate cancer if a biopsy is performed.3

• A PSA test can also be normal even when a man does have prostate cancer. This is called a “false negative” test. About 1 out of 7 men with PSA levels less than 4 have prostate cancer, which means 6 out of 7 do not.4 The higher a man’s PSA level is across all PSA ranges from zero on up, the more likely a man is to have prostate cancer. This is true even within the so-called “normal” range below 4.

• Prostate biopsies aren’t perfect tests, either. Prostate biopsies sometimes miss cancer when it’s there. Some doctors recommend a second set of biopsies if the first set is negative. Others will follow the PSA level and suggest more biopsies only if the level continues to go up. PROSD-A
If prostate cancer is found after a PSA test and a biopsy, common treatments are surgery to remove the prostate or radiation treatment to the prostate. Surgery has a very small risk of death. Both radiation and surgery can cause problems with urinary leakage in some men, but the risk of urinary leakage is higher with surgery. Both radiation and surgery cause problems with getting and keeping an erection in many men. The risk of problems with erections is higher with surgery in the short run, but over the long run, the risk is about the same with the two treatments. Radiation, though, also has a risk of causing bowel problems in some men. Some men, especially older men with slower-growing cancers, may not need treatments like surgery or radiation for their prostate cancer and can be followed with periodic PSA tests and physical exams, a process known as watchful waiting or active surveillance.
SUGGESTED “TALKING POINTS” TO COVER IN A DISCUSSION WITH A POTENTIAL SCREENEE ABOUT THE PROS AND CONS OF PSA TESTING

• It is not clear if screening a man with the PSA test lowers his chances of eventually dying of prostate cancer or helps him live longer. It is also not clear if screening a man with the PSA test lowers a man’s chances of eventually having to deal with complications of prostate cancer, such as painful spread of prostate cancer to the bones, but the lower rates of advanced-stage disease at the time of diagnosis and the lower rates of prostate cancer deaths suggest that fewer men may suffer from advanced disease. As a result, doctors disagree over the value of screening men with the PSA test. However it is well established that screening has been associated with an unprecedented shift in the stages of prostate cancer at the time of diagnosis. More than 75% of cancers are now detected when they are confined to the prostate gland, when current therapies are most effective. The actual relationship to PSA testing however remains unknown, but available evidence suggests that the lower mortality rates may be due, at least in part, to PSA testing. Special studies called randomized trials are the best way to determine how PSA testing affects the death rate from prostate cancer. Two of these long-term studies are underway in the US and Europe. Results are not expected for at least several years.5-7

• In summary, there are advantages and disadvantages to having a PSA test, and there is no “right” answer about PSA testing for everyone. Each man should make an informed decision about whether the PSA test is right for him.
SUGGESTED “TALKING POINTS” TO COVER IN A DISCUSSION WITH A POTENTIAL SCREENEE ABOUT THE PROS AND CONS OF PSA TESTING

- Frequency of biopsy complications with 10 core biopsy:
  - hematuria greater than 1 day - 14.5%
  - hematospermia - 37.4%
  - rectal bleeding < 2 days - 2.2%
  - prostatitis - 1.0%
  - epididymitis - 0.7%
  - fever > 38.5°C (101.3°F)- 0.8%
  - urinary retention - 0.2%
  - rectal bleeding > 2 days ± requiring surgical intervention- 0.7%
  - other complications requiring hospitalization- 0.3%
SUGGESTED “TALKING POINTS” TO COVER IN A DISCUSSION WITH A POTENTIAL SCREEENEE ABOUT THE PROS AND CONS OF PSA TESTING